Metabolic aspects of dietary sodium restriction as a therapeutic intervention

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Chapter 2

Rise in extracellular fluid volume during high sodium depends on BMI in healthy men

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Abstract

A high sodium (HS) intake is associated with increased cardiovascular and renal risk, especially in overweight subjects. We hypothesized that abnormal sodium and fluid handling is involved, independent of hypertension or insulin resistance.

Therefore, we studied the relation between BMI and sodium-induced changes in extracellular fluid volume (ECFV; distribution volume of 125I-iothalamate) in 78 healthy men, not selected for BMI. A total of 78 subjects with a median BMI of 22.5 (range: 19.2–33.9 kg/m^2) were studied after 1 week on a low sodium (LS) diet (50 mmol Na^+/24h) and after 1 week on HS (200 mmol Na^+/24h).

The change from LS to HS resulted in an increase in ECFV of 1.2 ± 1.8 L. Individual changes in ECFV were correlated to BMI ($R = 0.361$, $P < 0.01$). Furthermore, in response to HS, a higher BMI was associated to a higher rise in filtered load of sodium ($FLNa^+ = [Na+] \times GFR$, $R = 0.281$, $P < 0.05$).

Thus, a shift to HS leads to a larger rise in ECFV in healthy subjects with higher BMI, associated with an elevated $FLNa^+$ during HS. Although no hypertension occurred in these healthy subjects, our data provide a potential explanation for the interaction of sodium intake and BMI on cardiovascular and renal risk. Exaggerated fluid retention may be an early pathogenic factor in the cardiorenal complications of overweight.

Introduction

Several lines of evidence suggest an interaction between weight excess and high sodium (HS) intake on cardiovascular and renal risk profile. First, epidemiological studies have shown an association between high dietary sodium intake and an increased cardiovascular morbidity and mortality (1-3), that appears to be absent in lean subjects (4;5). In line, in the Prevention of Renal and Vascular Endstage Disease study an association between sodium intake and the cardiovascular and renal risk marker micro-albuminuria was found that was strong in overweight, and particularly obese subjects, but absent in lean subjects (6). Moreover, weight excess is well-known to be associated with the sodium sensitivity of blood pressure (7;8). Finally, we recently reported that HS elicits a renal hyperfiltration profile in overweight, but not lean young men (9). Together, these data suggest that weight excess modulates the adverse effects of excess sodium intake on cardiorenal risk profile.

The mechanism underlying this interaction has not been well established, but effects of weight excess on renal sodium handling and volume homeostasis are likely. In obese subjects with the metabolic syndrome tubular sodium reabsorption is increased (10). Moreover, hypertensive obese subjects have a higher extracellular fluid volume (ECFV) than non-obese subjects without hypertension (11). Metabolic syndrome and insulin resistance may well be involved in the association between weight excess and volume homeostasis (12), but data from our group demonstrate that renal effects of weight excess also occur independent of the metabolic syndrome and/or hypertension (9;13). Of note, the effects of BMI on renal risk profile are not limited to overt or morbid obesity, but extend well into the overweight range, i.e., a BMI between 25 and 30 kg/m^2, and perhaps even lower, thus extending to a considerable proportion of the population. To test the hypothesis that BMI is a determinant of volume homeostasis in healthy subjects we studied renal sodium handling and ECFV in 78 normal subjects in balance on low and high dietary sodium intake, respectively, and analyzed for a possible interaction between BMI and sodium homeostasis.

Materials and Methods

This study is a post hoc analysis from a larger study published earlier on the impact of BMI on the renal hemodynamic adaptation to HS intake (9). Recently, we showed that renal function assessment with the specific tracer ^{125}I-iothalamate could also be used for estimation of EFCV (14). The assessment of ECFV needs a single additional urine sampling that is not needed for glomerular filtration rate (GFR) assessment, to assess urinary excretion of ^{125}I-iothalamate during the run-in period. This additional sampling was available in 78/95 subjects, in whom,

accordingly, ECFV could be estimated. Only these 78 healthy men were included in the current analyses. The subset of 78 subjects was not different to the total population of 95 subjects in age, blood pressure, body weight, length, BMI, or ECFV (all $P > 0.5$). The study was approved by the local medical ethics committee, in accord with the Declaration of Helsinki Principles, and all participants gave written informed consent.

Study protocol

Subjects were studied at the end of two different 7-day periods, during which they used a low sodium (LS) diet (50 mmol Na^+/24h) and an HS diet (200 mmol Na^+/24h), respectively. Potassium intake was standardized at 80 mmol/24h. Otherwise, the subjects continued their usual food habits. For assessment of dietary compliance and sodium balance, 24-h urine was collected at day 4 and day 6 during each period. During both periods, the subjects were ambulant and continued their normal activities.

At day 7 of both study periods, the subjects reported at the research unit at 8 am hours, after having abstained from food and alcohol overnight. Height and body weight were measured at the start of this day. During the study day, subjects remained in a semisupine position except during voiding. One intravenous cannula was inserted in each forearm. One was used for infusion of tracers and the other for infusion of fluids and blood sample withdrawal. Blood was collected for fasting glucose and insulin determination. At 11 am, blood was withdrawn for determination of plasma renin activity and aldosterone. Sodium intake during the day was adjusted according to the actual diet in the concerning diet period. To ensure sufficient urine output, 250 mL of 5% glucose solution was administered in the right antecubital vein and subjects were provided with 250 mL of oral fluids every hour. After a 2 h run-in period, GFR and effective renal plasma flow were measured as the clearances of constantly infused ^{125}I-iothalamate and ^{131}I-hippuran, respectively. In this set-up, GFR is measured as the urinary clearance of ^{125}I-iothalamate, and corrected for voiding errors by the ratio of plasma to urinary clearance of ^{131}I-hippuran (15;16). ECFV is measured as the distribution volume of ^{125}I-iothalamate during steady state, as described in more detail recently. Briefly, the distribution volume of ^{125}I-iothalamalate is calculated from the plasma level of ^{125}I-iothalamate divided by the total amount of ^{125}I-iothalamate in the body, which equals the amount infused minus the amount excreted. It is calculated as $\text{sum}(I \times V) + \text{Bolus} - \text{sum}(U \times V)/P$, and expressed as ECFV/ body surface area (BSA), i.e., L/1.73 m^2 BSA. GFR, effective renal plasma flow, and ECFV measured as outlined above, has a day-to-day variation of 2.5, 5 and 9.2 %, respectively (14;16).

Blood pressure was assessed with an automatic device (Dinamap; GE Medical Systems,

Milwaukee, WI) at 15-min intervals. Mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure. Data on sodium handling were calculated as the mean of the two 1-h clearance periods, simultaneously with the GFR measurements. Fractional excretion of sodium was calculated as U × V/P of sodium divided by GFR and expressed as %. Filtered load ($FLNa^+$) was calculated as [Na^+] × GFR and tubular reabsorption of sodium ($TRNa^+$) as $FLNa^+$ minus urinary excretion; both were expressed in mmol/min.

Calculation of BSA and BMI

BSA and BMI were calculated from data obtained after a 1-week LS diet. BMI was calculated as body weight (in kg) divided by the square of height (m^2). BSA was calculated according to Dubois and Dubois: $0.007184 \times \text{height (cm)}^{0.725} \times \text{body weight (kg)}^{0.425}$ (17). ECFV is given indexed to 1.73 × BSA, to make comparison between subjects possible.

Chemical analysis of urine and blood samples

Urinary concentrations of sodium and potassium and blood concentrations of sodium and lipids (fasting) were measured by standard auto-analyser technique (MEGA; Merck, Darmstadt, Germany). Insulin was determined on an AxSym with a threshold of 1.0 μU/ml and intra-assay and interassay coefficients of variation of 2.6 and 4.3%, respectively (Abbott, Amstelveen, the Netherlands). Plasma glucose was determined by glucose-oxidase method (YSI 2300 Stat plus; Yellow Springs Instruments, Yellow Springs, OH, USA). Plasma renin activity was determined in terms of angiotensin I generation using a radioimmunoassay (18). Aldosterone was measured with a commercially available radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). As a measure for insulin resistance, the homeostatic model assessment index was calculated as (insulin (fasting plasma level) × glucose (fasting plasma level))/22.5 (19).

Data analysis

Data were analyzed using SPSS 14.0 (SPSS, Chicago, IL). Data were expressed as mean ± s.d. in text and tables and as mean ± s.e.m. in figure 1. Simple Pearson's parametric correlation was used for continuous analysis. Furthermore, the paired sample t-test was used for paired analyses (LS vs. HS), the independent samples' t-test for other parametric data and a Wilcoxon's signed rank test for other nonparametric data. Data on ECFV were analyzed both as crude values and after normalization for BSA. Since no essential differences between the two analyses were found, ECFV is only given normalized to BSA. A multivariate linear regression analysis was performed to asses whether BMI was determinant of ECFV independent of blood pressure, age, and renal hemodynamics.

Results

The study population consisted of 78 nonsmoking healthy normotensive white men, age 23 (21–25) years, (median (interquartile range)) not selected for BMI. All subjects had normal blood pressure, with a systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, both after LS and HS diet. All medical histories were without significant disease, and results of physical examination were unremarkable. In none of the subjects signs of diabetes or the metabolic syndrome were present. Height was 185 ± 7 cm; body weight during LS 79.0 ± 10.4 kg. Median BMI was 22.5, ranging from 19.0 to 33.7 kg/m^2.

Subject characteristics by BMI: effect of sodium intake

In table 1, subject characteristics are shown for measurements after 1-week LS and 1-week HS diet, and by a break-up by median BMI. Age was 23 (21–26) years and 23 (21–25) years for the low and high BMI group, respectively. No differences in blood pressure, fasting glucose, insulin, homeostatic model assessment index, serum cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides were found between the subgroups with highest and lowest BMI. Blood pressure rose significantly when shifting from LS to HS (mean arterial pressure: 86 ± 7 vs. 88 ± 7 mmHg, respectively, P <0.01), however, without differences between the BMI groups.

Adherence to the sodium diet was good and equal between the BMI groups. Serum [Na^+] rose significantly when shifting from LS to HS (138 ± 3 vs. 139 ± 3 mmol/L respectively, p = 0.01), without differences between the BMI groups. During LS intake, all parameters of renal function and sodium handling, as well as ECFV/1.73 m^2, were similar between the groups. However, during HS, significant differences in renal sodium handling and volume status emerged between the groups. ECFV/1.73 m^2 was significantly higher in the higher BMI group, i.e., 16.7 ± 1.4 vs. 18.1 ± 1.6 L/m^2 (P < 0.001) as also illustrated in figure 1. Renal sodium handling was different between the groups during HS only, with a higher $FLNa^+$ in the higher BMI group, mainly related to the significantly higher GFR. $TRNa^+$ was higher as well; $FENa^+$ was lower in the higher BMI group, but this difference did not reach statistical significance (p = 0.1).

In table 2, the sodium-induced changes in renal sodium handling and ECFV are summarized. The shift from low to HS elicited a modest rise in ECFV (P <0.05) in the lower BMI group with a significantly larger rise in ECFV (p <0.01 low vs. high BMI group) in the higher BMI group. $FLNa^+$ increased more in the higher BMI group, reflecting a larger rise in GFR (+12.3 ± 9.8 vs. +6.7 ± 12.0 mL/min in the lower BMI group, p = 0.02) and larger rise in FF (+0.97 ± 2 vs. -0.16 ± 2%, p = 0.03) in that group. $TRNa^+$, expressed in mmol/min also increased more in the

Table 1: Characteristics after 1-week low sodium and 1-week high sodium diet according to median BMI

	Low sodium intake		High sodium intake	
	BMI < median	BMI > median	BMI < median	BMI > median
MAP (mmHg)	85 ± 6	88 ± 8	87 ± 7	89 ± 6
Body Weight (kg)	73.4 ± 6.2	84.5 ± 10.8*	74.6 ± 6.4	86.0 ± 10.9*
Height (cm)	186 ± 6	185 ± 7	-	-
BMI (kg/m^2)	21.1 ± 0.9	24.6 ± 2.5*	21.5 ± 0.9	25.0 ± 2.5*
Glucose (mmol/L)	4.7 ± 0.7	4.6 ± 0.7	4.6 ± 0.6	4.5 ± 0.5
Insulin (mU/L)	11.1 ± 6.7	10.2 ± 4.9	9.4 ± 4.3	9.9 ± 5.3
HOMA	2.4 ± 1.7	2.1 ± 1.1	1.9 ± 1.0	2.0 ± 1.2
Total cholesterol (mmol/L)	4.3 ± 0.8	4.2 ± 0.6	4.1 ± 0.8	4.2 ± 0.7
Triglycerides (mmol/L)	1.2 ± 0.6	1.2 ± 0.6	1.1 ± 0.6	1.1 ± 0.5
HDL-cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3
LDL-cholesterol (mmol/L)	2.6 ± 0.6	2.5 ± 0.6	2.4 ± 0.6	2.6 ± 0.6
Na^+ excretion (mmol/24h)	38 ±25	37 ±21	241 ±68	243 ±61
Serum [Na^+] (mmol/L)	138 ± 3	139 ± 3	139 ± 3	140 ± 3
ECFV (L*m^{-2}*1.73)	16.3 ± 1.8	16.7 ± 1.4	16.7 ± 1.4	18.1 ± 1.6*
FLNa+ (mmol/min)	17.4 ± 2.2	18.4 ± 2.6	18.5 ± 2.3	20.2 ± 2.7*
TRNa+ (mmol/min)	17.3 ± 2.2	18.3 ± 2.6	18.1 ± 2.3	19.9 ± 2.8*
FENa+ (%)	0.51 ± 0.4	0.45 ± 0.4	1.75 ± 0.6	1.52 ± 0.7
GFR (ml/min)	125 ± 16	132 ± 18	131 ± 15	145 ± 18*
PRA (ng Ang-I/mL/h)	6.4 ± 3.2	6.5 ± 3.6	2.3 ± 1.2	2.3 ± 1.2
Aldosterone (ng/L)	135 ± 71	160 ± 104	46 ± 26	42 ± 28

Abbreviations: ECFV: extra cellular fluid volume, GFR: glomerular filtration rate, $FENa^+$: fractional excretion of sodium, $FLNa^+$: filtered load of sodium, HOMA: homeostatic model assessment, MAP: mean arterial pressure, PRA: plasma renin activity, $TRNa^+$: tubular reabsorption of sodium. *p < 0.01 low vs. high BMI group.

highest BMI group. Thus, the sodium induced increase in $TRNa^+$ was, in parallel to the increase in $FLNa^+$, higher in the highest BMI group. As a measure for relative blunting of tubular reabsorption, $FENa^+$ rose less in the highest BMI group, but this finding did not reach statistical significance (p = 0.12).

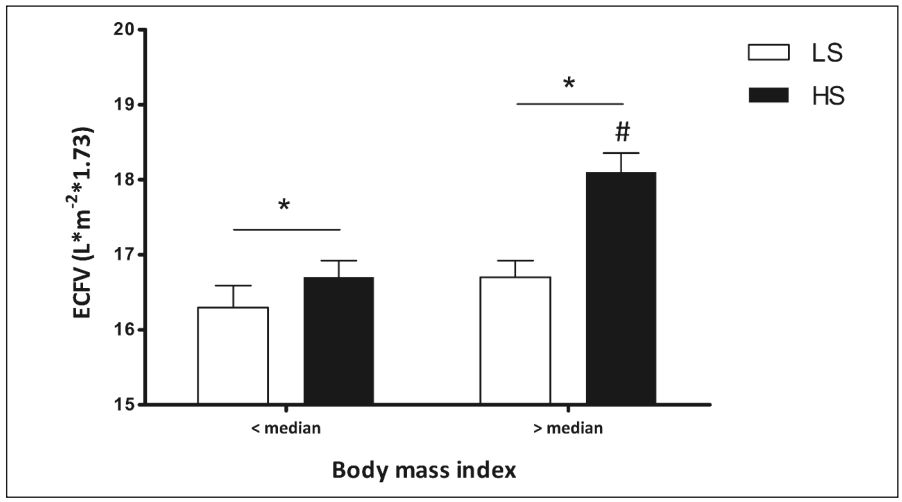

*Figure 1: Values for extra cellular fluid volume (ECFV), for respectively low and high dietary sodium intake shown for a break-up according to median BMI. *p < 0.01 low vs. high sodium intake. #p < 0.01 BMI below vs. above median. HS, high sodium; LS, low sodium.*

Table 2: Sodium-induced changes shown according to median BMI with in the right column the correlation coefficient (R) for the univariate correlation with BMI

	sodium induced changes		Correlation (*R*) with BMI
	BMI < median	BMI > median	
Δ ECFV (L*m-2*1.73)	0.5 ± 1.6	1.5 ± 1.5*	0.361**
Δ $FLNa^+$ (mmol/min)	1.0 ± 1.6	1.9 ± 1.3*	0.329**
Δ $TRNa^+$ (mmol/min)	0.8 ± 1.6	1.7 ± 1.2*	0.341**
Δ $FENa^+$ (%)	1.25 ± 0.6	1.12 ± 0.6	-0.210

ECFV: extra cellular fluid volume, $FENa^+$: fractional excretion of sodium, $FLNa^+$: filtered load of sodium, $TRNa^+$: tubular reabsorption of sodium.*p < 0.05 low vs. high BMI group. **p < 0.05 for continuous univariate correlation with BMI.

BMI as a determinant of ECFV during HS intake

A higher BMI significantly correlated to a larger rise in ECFV (R = 0.361, P <0.01) as shown in figure 2 and table 2, right column. The correlation was still significant after exclusion of the two subjects with a BMI >30 kg/m^2 (n = 76; R = 0.328, p<0.01). These univariate data were confirmed on multivariate analysis. In the model, with an R^2 of 0.131, BMI was the only significant predictor of the change in ECFV (β = 0.361, p < 0.01) as dependent variable; forced entry of blood pressure, age, and renal hemodynamics did not improve the model. Furthermore,

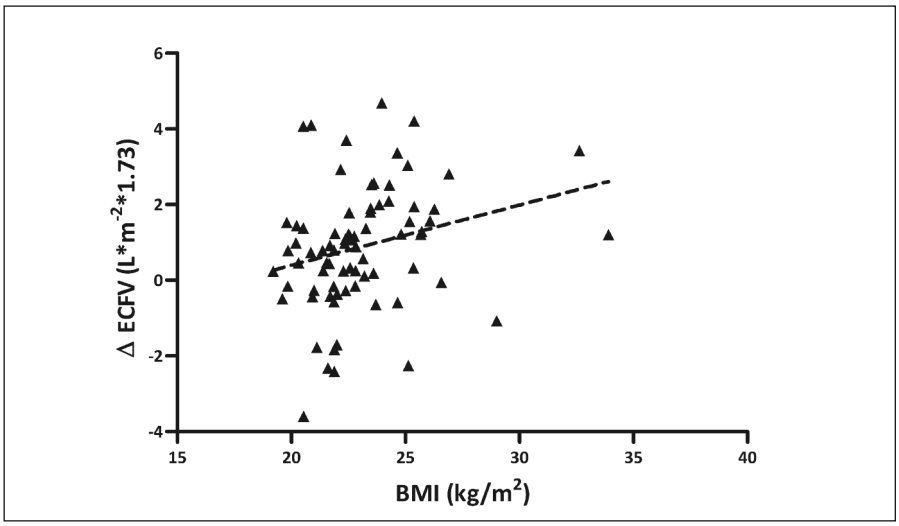

Figure 2: Scatterplot for the shift in extra cellular fluid volume (ECFV) from low sodium to high sodium intake vs. BMI. R = 0.361, P < 0.01.

as shown in table 2, BMI correlated with a larger sodium-induced change in $FLNa^+$ ($R = 0.281$, $p < 0.05$) and in $TRNa^+$ ($R= 0.293$, $p < 0.05$), but not to the change in $[Na^+]$ or mean arterial pressure. Correlations with the changes in $FENa^+$ did not reach statistical significance. During LS diet, $FLNa^+$, $TRNa^+$, and $FENa^+$ did not correlate to BMI. During HS however, a higher $FLNa^+$ (0.356, $p < 0.01$), a higher $TRNa^+$ ($R = 0.373$, $p < 0.01$), and a lower $FENa^+$ ($R = -0.263$, $p < 0.05$) was significantly correlated to a higher BMI.

Results on correlations between BMI and sodium-induced renal hemodynamic changes presented in earlier report (9) were reproduced in the subset used for this study, namely a correlation between BMI and a sodium-induced rise in GFR ($R = 0.233$, $p < 0.05$) and in FF ($R = 0.274$, $p < 0.05$); BMI was not related to the sodium-induced rise in effective renal plasma flow.

Discussion

This study is the first to demonstrate that BMI determines the response of ECFV to a rise in sodium intake in healthy young adults. The rise in ECFV in response to an HS diet was larger in subjects with a higher BMI, even in the absence of overt obesity, or hypertension. As a consequence, during HS intake ECFV/BSA was significantly higher in overweight subjects than in lean subjects, whereas during LS diet it was not different. Our data suggest that effects

of BMI on volume regulation may be involved in the combined effects of weight excess and sodium intake in long-term cardiovascular risk in epidemiological studies.

Our study was performed in healthy young men. To be able to dissect the effects of a higher BMI as such from those of its complications, hypertension and diabetes were exclusion criteria. Moreover, none of the subjects in our study met the criteria of the metabolic syndrome, and homeostatic model assessment was normal in all subjects, suggesting that insulin resistance was not involved. The effects on sodium homeostasis thus appear to be related to the higher BMI per se rather than to any of its complications. Our population was not selected for weight excess, median BMI was 22.5 kg/m^2, and only two subjects were obese. Thus, the weight excess in our population was not particularly prominent and it is remarkable that clear-cut effects on volume status could nevertheless be observed. Yet, this is consistent with data demonstrating that the association between young adult BMI, metabolic risk factors, and long-term risk also extends to the range of BMI <25 (9;13;20;21).

Altered sodium handling and volume excess have been reported previously in overt obesity and the metabolic syndrome (11;12;22-25). In the Olivetti study, obesity and the metabolic syndrome were associated with increased tubular sodium reabsorption as well as hypertension (10;12), and Chagnac reported altered tubular sodium handling in severely obese subjects (24;25). Our study is the first to demonstrate BMI-dependent altered volume homeostasis in the absence of overt obesity, i.e., in the overweight range, in healthy young adults. Apparently, overt obesity or presence of the metabolic syndrome is not a prerequisite for BMI-dependent alterations in sodium status. This is consistent with the assumption that abnormal renal sodium may be a causal factor in overweight-associated morbidity rather than a consequence.

In our study, the effects of BMI on volume status were not associated with an effect on blood pressure. Apparently in these normotensive subjects, blood pressure was not volume-dependent - at least not over the range of volume change investigated here - and peripheral vasodilatation accounted for a stable blood pressure despite a higher ECFV. The absence of an association with higher blood pressure allows to conclude that the altered sodium handling was not secondary to the presence of hypertension in subjects with higher BMI. This is relevant to note, as most observations on altered sodium handling in obesity were made in hypertensive conditions, be it in animal studies or in humans (10;12;22;24-27).

What could be the clinical relevance of an effect on sodium status without a blood pressure effect? Several lines of evidence support adverse effects of HS intake that are independent of blood pressure. For instance, the association between HS intake and left ventricular hypertrophy is only partly dependent on blood pressure (28). Moreover, several epidemiological studies have shown an association between sodium intake and cardiovascular

morbidity and mortality that is independent of blood pressure (2;3). Remarkably, this also accounts for the combined effects of BMI and sodium intake on long-term outcome (4;5). Excess expansion of ECFV, and its consequent volume load for the heart would be a plausible candidate mechanism underlying blood pressure independent effects of HS intake. As ECFV is not usually measured, however, data to directly support this assumption are lacking.

It would be interesting to know whether regulation of ECFV is also involved in normal weight sodium sensitive hypertension. Moreover, salt sensitivity of blood pressure is associated with altered renal sodium handling (29) and with a rise in filtration fraction and glomerular hypertension elicited by HS diet, which is remarkably similar to our prior findings in overweight subjects (9). Unfortunately, as mentioned above, ECFV is not usually measured in studies on sodium sensitivity. Moreover, although salt sensitivity is strongly associated with overweight (7;8), in most studies BMI is either not reported or not considered in the data analysis (30;31). Therefore, is it difficult at this point in time to establish whether sodium sensitivity as such, independent of BMI, is associated with volume expansion, leaving this issue unsolved, yet, it would be an important issue to address in future studies.

We previously reported on the effect of BMI on the renal hemodynamic response to HS intake (9). Our current report addresses the concomitant effects on ECFV in a large subset of this population. The effects on renal hemodynamics in this subset were fully in line with those of the whole population, namely a more pronounced rise in GFR in the subjects with the higher BMI. In fact, the impact of BMI on the responses of GFR and ECFV to HS was strikingly similar, suggesting that the more pronounced rise in GFR in the overweight subjects might be due to the more pronounced rise in ECFV. In this concept, overweight associated hampered suppression of tubular reabsorption would be the primary phenomenon, and the exaggerated rise in ECFV and GFR its consequence, allowing the achievement of sodium balance by a larger increase in filtered load.

This study has several limitations. First, we used BMI as a measure for adipose tissue, although it is only an indirect assessment. Second, we approximated renal sodium handling by measuring the fractional excretion of sodium. However, these data do not allow us to dissect between proximal and distal tubular sodium handling. Moreover, it should be mentioned that ECFV is directly related to body dimensions. Thus, differences between individuals should be interpreted with caution as these are less robust than those on the within-individual sodium-induced changes. Furthermore, in this study only young male subjects were included. Therefore, extrapolation to female subjects may not be warranted. Finally it should be mentioned that we investigated ECFV after only 1 week of altered sodium intake. Whereas this was sufficiently long to achieve sodium balance again, it is unknown whether the differences observed here persist during long-term follow-up.

From our data, it could be hypothesized that an LS intake could have the potential to prevent part of the cardiovascular and/or morbidity associated with weight excess, but long-term data would be needed to substantiate this assumption. We conclude that in young healthy men a higher BMI is associated with a larger increase in ECFV during HS intake. These data suggest that altered sodium and fluid handling may be an early phenomenon in the pathophysiological consequences of weight excess, and that dietary sodium restriction may have preventive potential in overweight subjects.

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